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Prediction of solubility of practically insoluble drugs in water/ethanol solvents using non-empirical methods

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ABSTRACT

The solubilities of ibuprofen and diazepam in water/ethanol binary solutions were predicted using COSMO-RS and UNIFAC. In case of the ibuprofen system, RMSE was 0.183, and COSMO-RS reproduced the experimental values well. The RMSE of UNIFAC was 0.628, and the solubilities predicted by UNIFAC were smaller than experimental values. Polarizabilities of several drugs in vacuum, water, and ethanol were calculated. A linear correlation between polarizabilities and solubilities was observed to exist in water.

Keywords: COSMO-RS, UNIFAC. Prediction of solubility, co-solvent, polarizability.

INTRODUCTION

One of the fundamental features of drugs is their solubility[1]; it serves an essential role in drug disposition. The organic synthesis of a drug molecule often involves numerous synthetic steps. Every year, the number of potential drug candidates and associated intermediates continues to increase. Even after the drug is synthesized, researchers spend considerable amounts of time finding suitable solvents. The use of a predictive property method can reduce both time and cost and significantly enhance the success of developing and manufacturing a new drug. For instance, in addition to enhancing the solubility of ethanol or an ethanol aqueous solution, it can affect a drug's absorption, distribution, metabolism, and excretion. Previous researchers have used empirical approaches involving 2D topological [2] and 3D descriptors [3] in artificial neural networks for predicting solubilities of drugs in water and mono-solvents.

However, few studies have predicted the solubilities of drugs in mixed solvents. In this study, we aim to predict solubilities of drugs using the conductor-like screening model for realistic solvation (COSMO-RS) method [4-5]. For comparison purposes, we have also used the group

contribution method[6]. In addition, it was demonstrated that polarizability is important in the modeling of solubility (Dyer et al.).[7]

We determined the frequency-dependent polarizabilities of drugs using DFT calculation and studied the relationship between polarizabilities and solubilities of drugs.

EXPERIMENTAL SECTION

COSMO-RS method

We assumed that all relevant interactions of the perfectly screened molecules can be expressed as local contact energies and can be quantified by the local polarization charge densities of the contacting surfaces.

For the mixtures the activity coefficient of a compound i in a mixtures S can be calculated as

$$\gamma_i^*(S;T) = \exp\left\{\frac{\mu_i^*(S;T) - \mu_i^*(i;T)}{kT}\right\} \quad (1)$$

Where $\mu_i^*(i;T)$ refers to the pseudo-chemical potential of the compound *i* in the pure liquid i.

For the calculation between solids and the liquid phase, the free energy of melting, $\Delta G_{,\text{melt}}$ is usually determined by Equation (2),

$$\mu^{sol}{}_i(T) - \mu^*{}_i(i,T) = \Delta G \cong (\Delta H_{\text{fus}} + T_{\text{fus}}\Delta c_{p,\text{fus}})\left(1 - \frac{T}{T_{\text{fus}}}\right) + T_{\text{fus}}\Delta c_{p,\text{fus}} \ln\left(\frac{T}{T_{\text{fus}}}\right) \quad (2)$$

where $\mu^{sol}{}_i(T)$ is chemical potential of the pure liquid ; $\mu^*{}_i(i,T)$ is chemical potential of the pure liquid; $\Delta H_{,\text{melt}}$ is the enthalpy of melting; $\Delta C_{p,\text{melt}}$ is change in the heat capacity, and T_{melt} is re melting temperature. For temperatures reasonably close to the melting point, $\Delta C_{p,\text{melt}}$ often can be neglected.

The gas-phase geometries of a molecule are optimized by using the density-functional theory (DFT) with the Becke-Perdew (BP) and Triple-Zeta Polarized (TZP) basis set. Similarly, the solvent crs calculation is performed with BP/TZP level of theory and generation of input data of the COSMO-RS. DFT calculations were performed using the ADF program [8]. The activity coefficients of the solutes were calculated using the COSMO-RS module in the ADF program.

Group contribution method

The activity coefficient in UNIFAC is represented as an additive-constitutive parameter. It is estimated as the product of a combinatorial part and a residual part.

$$\ln\gamma_i = \ln\gamma_i^C + \ln\gamma_i^R \ , \quad (3)$$

where γ_i is the activity coefficient of solute *i*; γ_i^C is its combinatorial part, and γ_i^R is its residual part.

The γ_i^C is the contributed part of the activity coefficient based on molecular shape and molecular volume, and is represented by Equation (4)

$$\ln \gamma_i^C = \ln \frac{\phi_i}{x_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\phi_i} + l_i - \frac{\phi_i}{x_i} \sum_i x_j l_j \qquad (4)$$

where ϕ_i is volume fraction for the *i* molecule; θ_i is area fraction for the *i* molecule; l_i is a compound parameter of *r*(volume), *z* and *q*(surface), and z is the coordination number of the system.

The γ_i^R is the contributed part of the activity coefficient based on interaction, and is represented by Equation (5)

$$\ln \gamma_i^R = \sum_k \nu_k^{(i)} \left\{ \ln \Gamma_k - \ln \Gamma_k^{(i)} \right\} \qquad (5)$$

where $\nu_k^{(i)}$ is the number of groups of the type k in *i* molecule ; Γ_k is the residual activity coefficient of group *k* in the solution, and $\Gamma_k^{(i)}$ is the residual activity coefficient of group *k* in a reference solution containing only *i* molecule.

RESULT AND DISCUSSION

The mole fraction solubilities of ibuprofen and diazepam in water/ethanol binary solvent predicted using COSMO-RS or UNIFAC, are listed along with their experimental values[9,10] in Table 1 and 2.

Table 1. Predicted solubilities of ibuprofen in water/ethanol mixed solvent using cosmo-rs and UNIFAC

x_{ETOH}	predicted *s* (COSMO-RS)	predicted *s*(UNIFAC)	Experimental *s**
0	8.540×10^{-6}	2.376×10^{-6}	1.346×10^{-5}
0.04170	3.302×10^{-5}	7.959×10^{-6}	2.140×10^{-5}
0.08918	1.129×10^{-4}	2.563×10^{-5}	7.054×10^{-5}
0.1	2.009×10^{-4}	3.660×10^{-5}	
0.2	0.001344	2.800×10^{-4}	
0.3	0.004623	0.001360	
0.3701	0.01648	0.003453	0.03107
0.4	0.02503	0.004750	
0.4775	0.04762	0.01139	0.09168
0.5	0.05660	0.01310	
0.6	0.1102	0.03002	
0.6104	0.1104	0.003327	0.1462
0.7	0.1587	0.05948	
0.7790	0.1887	0.008840	0.02074
0.8	0.1961	0.1048	
0.9	0.2240	0.1680	
1	0.2242	0.2487	0.02411

* References 9

Table 2. Predicted solubilities of diazepam in water/ethanol mixed solvent using COSMO-RS

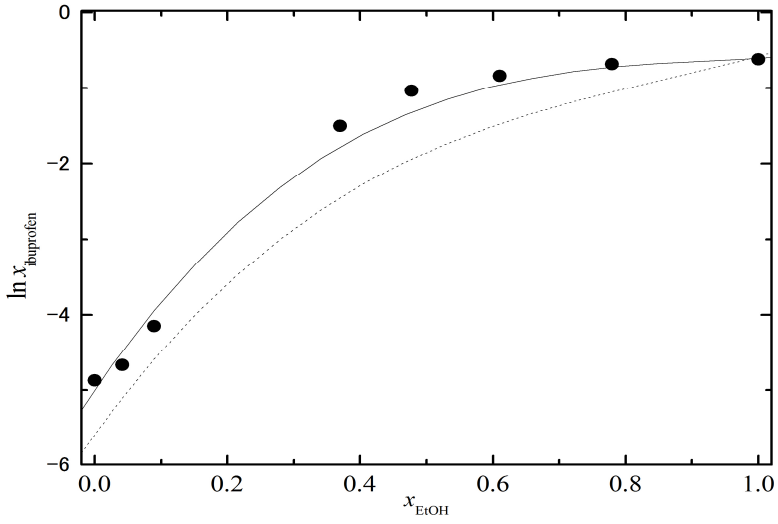
x_{ETOH}	predicted s(COSMO-RS)	Experimental s*
0	1.791×10^{-5}	6.886×10^{-6}
0.03323	2.981×10^{-5}	1.812×10^{-5}
0.07178	6.044×10^{-5}	3.470×10^{-5}
0.1000	7.143×10^{-5}	
0.1170	1.289×10^{-4}	9.505×10^{-5}
0.1709	3.224×10^{-4}	3.224×10^{-5}
0.2000	4.562×10^{-4}	
0.2362	6.648×10^{-4}	8.259×10^{-4}
0.3000	0.001478	
0.3169	0.001550	
0.4000	0.003206	0.001969
0.4192	0.003458	0.003867
0.5000	0.005336	
0.5530	0.006681	0.005315
0.6000	0.007365	
0.7000	0.008816	
0.7357	0.009374	0.007324
0.8000	0.009380	
0.9000	0.008951	
1	0.007589	0.005187

* References 10

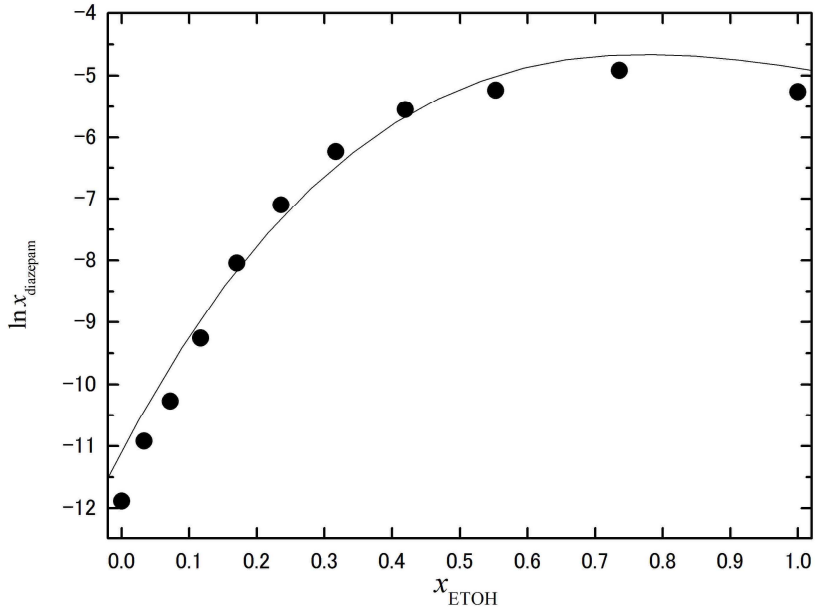
The smoothed values of logarithmic mole fraction solubilities are calculated by Equation (6), and plotted against the mole fractions of ethanol(x_{EtOH}) in Graph. -1 and -2.

$$\log x_{drug} = A0 + A1x_{EtOH} + A2\ x_{EtOH}^2 + A3\ x_{EtOH}^3 \qquad (6)$$

Graph-1. Logarithmic experimental (●) (Manrique al., 2007) mole fraction solubilities, predicted using COSMO-RS (solid lines) and predicted using UNIFAC (dotted line) mole fraction solubilities of ibuprofen in the mixed solvent water/ethanol are plotted against the mole fraction of ethanol at 298.15 K



Graph.-2. Logarithmic experimental (●) (Shayanfar et al., 2009) and predicted using COSMO-RS (solid lines) mole fraction solubilities of diazepam in the mixed solvent water/ethanol are plotted against the mole fraction of ethanol at 298.15 K



In order to the accuracy of the predicted logarithmic solubilities, the root mean square error (RMSE) which is defined in Equation(7)[11] and the average absolute error(AAE) which is defined

$$RMSE = \sqrt{\frac{\sum (observed - predicted)^2}{n}} \quad (7)$$

$$AAE = \frac{\sum |observed - predicted|}{n} \quad (8)$$

in Equation (8) [11]were calculated and listed in Table 3.

Table 3. The root mean square error (RMSE) and the average absolute error (AAE) of predicted logarithmic mole fraction solubility in water/ethanol mixtures

drug	method	RMSE	AAE
Ibuprofen	COSMO-RS	0.183	0.157
	UNIFAC	0.628	0.556
Diazepam	COSMO-RS	0.411	0.337

In the diazepam system, the RMSE and AAE were 0. 411 and 0.337 respectively, and the COSMO-RS reproduced the experimental values accurately, as in the case of ibuprofen. The group contribution parameter of diazepam was nonexistent in the UNIFAC program, and the solubilities of diazepam could not be predicted using UNIFAC.

As observed from Equation (1), even COSMO-RS, which is a theoretical method, required experimental values. However, the prediction of solubilities using polarizabilities did not require experimental values.

To confirm the applicability of drug solubilities, the frequency-dependent polarizabilities of drug-like compounds were calculated at b3lyp/6-31g** levels using Gaussian 09 program[12] and listed in Table 4, calculated using a dielectric continuum model .

Table 4. Calculated polarizabilities of drug-like compounds in water

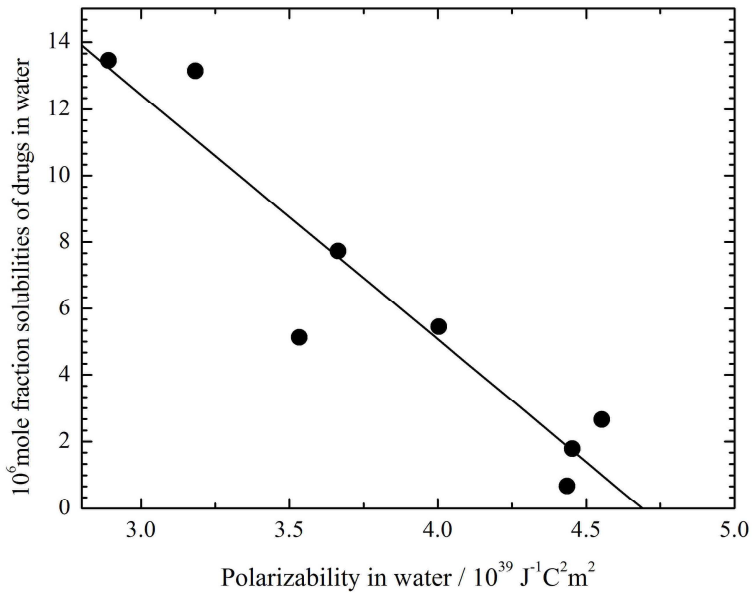
Compounds	Polarizability / $10^{39} C^2 m^2 J^{-1}$	Polarizability / $10^{39} C^2 m^2 J^{-1}$
	Calculation	Reference
Aniline	1.3764	1.3463
Anisole	1.4968	1.4576
Benzene	1.1477	1.1127
Phenol	1.3764	1.2350
Pyridine	1.0462	1.0214

These calculated values of the polarizabilities are slightly smaller than their reference values[13,14,15] and are observed to be qualitatively accurate. The polarizabilities of molecules can be estimated sufficiently well using this method.

The polarizabilities of several drugs were similarly calculated; these values are listed in Table 5. In addition, they are plotted against the polarizabilities of these drugs along with experimental solubitities[10,16,17,18,19,20] in water and in ethanol in Graph 3 and 4 respectively. A linear correlation between polarizabilities and solubilities was observed to exist in water.

For the sake of comparison, calculated solubility parameters of drugs and Hydrophile-Lipophile Balance (HLB) of drugs using software [21] are listed in Table 6. In addition, they are plotted against the polarizabilities of these drugs along with experimental solubitities[10,16,17,18,19,20]in water in Graph 5 and 6.

Graph -3. Mole fraction solubilities of drugs in water plotted ageinst the polarizabilities of drugs in water 298.15 K



Graph -4. Mole fraction solubilities of drugs in ethanol plotted ageinst the polarizabilities of drugs in ethanol at 298.15K

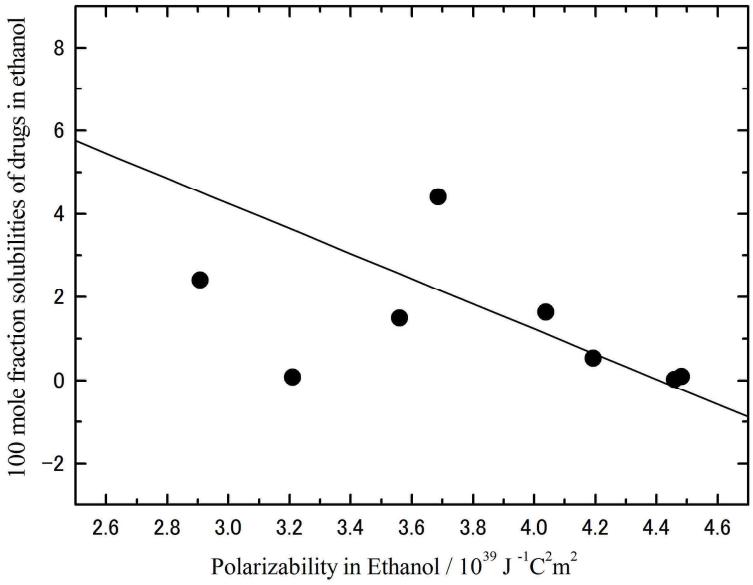


Table 5. Calculated polarizabilities of drugs in water and in ethanol

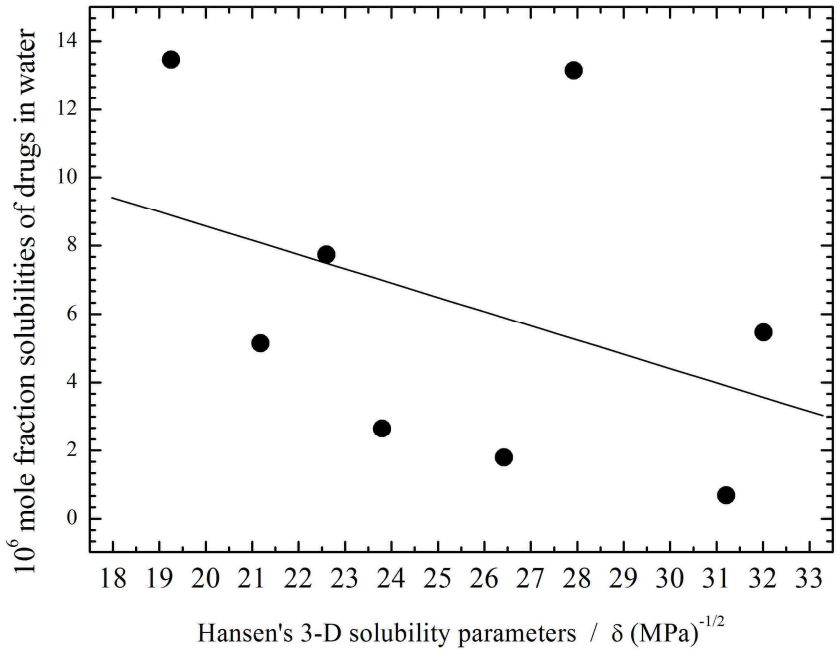
Compounds	Polarizability $10^{39}C^2m^2J^{-1}$	Polarizability $10^{39}C^2m^2J^{-1}$
	in water	in ethanol
Apigenin[16]	4.436	4.459
Clonazepam[10]	4.453	4.481
Diazepam[10]	4.553	4.193
Ibuprofen[17]	2.908	2.891
Ketoprofen [18]	3.664	3.687
Lamotrigine [10]	3.183	3.210
Naproxen [19]	3.533	3.559
Niflumic Acid[20]	4.038	4.003

Table 6. Solubility parameter(SP) and Hydrophile-Lipophile Balance(HLB) of drugs

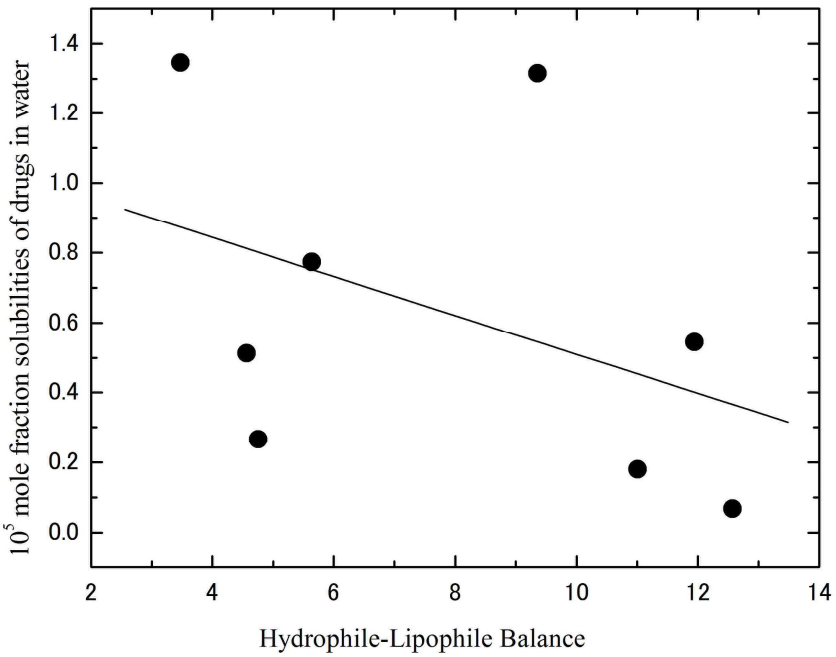
Compounds	SP / δ(MPa)$^{1/2}$	HLB
Apigenin	31.2	12.6
Clonazepam	26.4	11.0
Diazepam	23.8	4.8
Ibuprofen	19.3	3.5
Ketoprofen	22.6	5.6
Lamotrigine	27.9	9.4
Naproxen	21.2	4.6
Niflumic Acid	32.0	11.9

It seems that the prediction method using the polarizabilities of molecules reproduce the experimental solubilities in water compare with other two prediction methods.

Graph -5. Mole fraction solubilities of drugs in water plotted against the Hansen's 3-D solubility parameter at 298.15K



Graph-6. Mole fraction solubilities of drugs in water plotted ageinst the Hydrophile-Lipophile Balance at 298.15K



CONCLUSION

Experimental solubilities of ibuprofen and diazepam in water/ethanol binary solvent were reproduced well using COSMO-RS as compared to those reproduced using UNIFAC.

It is difficult to predict the experimental solubilities of drugs quantitatively; nevertheless, a linear correlation can be observed between polarizabilities and solubilities. It seems that the non-empirical prediction method using the polarizabilities of molecules reproduce the experimental solubilities in water.

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